**Arthritis & Rheumatology**
Vol. 73, No. 4, April 2021, pp 677–686
DOI 10.1002/art.41566


American College of Rheumatology
*Empowering Rheumatology Professionals*

# Risk Prediction Modeling Based on a Combination of Initial Serum Biomarker Levels in Polymyositis/Dermatomyositis–Associated Interstitial Lung Disease

Takahisa Gono,[1] Kenichi Masui,[2] Naoshi Nishina,[3] Yasushi Kawaguchi,[4] Atsushi Kawakami,[5] Kei Ikeda,[6] Yohei Kirino,[7] Yumiko Sugiyama,[8] Yoshinori Tanino,[9] Takahiro Nunokawa,[10] Yuko Kaneko,[3] Shinji Sato,[11] Katsuaki Asakawa,[12] Taro Ukichi,[13] Shinjiro Kaieda,[14] Taio Naniwa,[15] Yutaka Okano,[16] Masataka Kuwana,[1] and the Multicenter Retrospective Cohort of Japanese Patients with Myositis-Associated ILD (JAMI) Investigators

**Objective.** To establish predictive models for mortality in patients with polymyositis/dermatomyositis–associated interstitial lung disease (PM/DM-ILD) using a combination of initial serum biomarker levels.

**Methods.** The Multicenter Retrospective Cohort of Japanese Patients with Myositis-Associated ILD (JAMI) database of 497 incident cases of PM/DM-ILD was used as a derivation cohort, and 111 cases were additionally collected as a validation cohort. Risk factors predictive of all-cause mortality were identified by univariate and multivariable Cox regression analyses using candidate serum biomarkers as explanatory variables. The predictive models for mortality were generated in patients with and those without anti–melanoma differentiation–associated gene 5 (MDA-5) antibody, using a combination of risk factors. Cumulative survival rates were assessed using Kaplan-Meier analysis, and were compared between subgroups using the Breslow test.

**Results.** In the derivation cohort, C-reactive protein (CRP) and Krebs von den Lungen 6 (KL-6) levels were identified as independent risk factors for mortality in both anti–MDA-5–positive and anti–MDA-5–negative patients. We then developed a prediction model based on anti–MDA-5 antibody status, CRP level, and KL-6 level, termed the "MCK model," to identify patients at low (<15%), moderate (15–50%), or high (≥50%) risk of mortality, based on the number of risk factors. The MCK model successfully differentiated cumulative survival rates in anti–MDA-5–positive patients ($P < 0.01$ for low versus moderate risk and $P = 0.03$ for moderate versus high risk) and in anti–MDA-5–negative patients ($P < 0.001$ for low versus moderate risk). The utility of the MCK model was replicated in the validation cohort.

**Conclusion.** Our findings indicate that an evidence-based risk prediction model using CRP and KL-6 levels combined with anti–MDA-5 antibody status might be useful for predicting prognosis in patients with PM/DM-ILD.

Supported in part by a research grant from the Japanese Ministry of Health, Labor, and Welfare and a research grant from Astellas Pharma.

[1]Takahisa Gono, MD, PhD, Masataka Kuwana, MD, PhD: Nippon Medical School Graduate School of Medicine, Tokyo, Japan; [2]Kenichi Masui, MD: National Defense Medical College School of Medicine, Saitama, Japan, and Show University Hospital, Tokyo, Japan; [3]Naoshi Nishina, MD, PhD, Yuko Kaneko, MD: Keio University School of Medicine, Tokyo, Japan; [4]Yasushi Kawaguchi, MD, PhD: Tokyo Women's Medical University, Tokyo, Japan; [5]Atsushi Kawakami, MD, PhD: Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan; [6]Kei Ikeda, MD, PhD: Chiba University Hospital, Chiba, Japan; [7]Yohei Kirino, MD, PhD: Yokohama City University Graduate School of Medicine, Yokohama, Japan; [8]Yumiko Sugiyama, MD, PhD: Yokohama City University Medical Center, Yokohama, Japan; [9]Yoshinori Tanino, MD, PhD: Fukushima Medical University School of Medicine, Fukushima, Japan; [10]Takahiro Nunokawa, MD: Tokyo Metropolitan Tama Medical Center, Tokyo, Japan; [11]Shinji Sato, MD: Tokai University School of Medicine, Kanagawa, Japan; [12]Katsuaki Asakawa, MD: Niigata University Medical and Dental Hospital, Niigata, Japan; [13]Taro Ukichi, MD, PhD: The Jikei University School of Medicine, Tokyo, Japan; [14]Shinjiro Kaieda, MD: Kurume University School of Medicine, Fukuoka, Japan; [15]Taio Naniwa, MD, PhD: Nagoya City University School of Medicine, Aichi, Japan; [16]Yutaka Okano, MD: Kawasaki Municipal Hospital, Kawasaki, Japan.

Drs. Gono and Masui contributed equally to this work.

Dr. Kawakami has received consulting fees, speaking fees, and/or honoraria from AbbVie, Actelion, Asahi Kasei, Astellas, AstraZeneca, Alexion, Boehringer Ingelheim, Bristol Myers Squibb, Chugai, Cosmic, Daiichi Sankyo, Eisai, Eli Lilly, Kissei, Janssen, Kowa, Kyowa Kirin, Mitsubishi Tanabe, Mochida, MSD, Nihon Medi-Physics, Nippon Kayaku, Novartis, Pfizer, Ono, Otsuka, Sanofi, Sumitomo Dainippon, Taisho Toyama, Takeda, Teijin, UCB, and YI Biologics (less than $10,000 each) and research grants from those companies. Drs. Sato and Kuwana hold the patent for the anti–MDA-5 antibody measurement kit that was used in this study. Dr. Kuwana has received consulting fees, speaking fees, and/or honoraria from AbbVie, Actelion, Asahi Kasei, Astellas, Boehringer Ingelheim, Bayer, Chugai, Eisai, Corbus, CSL Behring, Janssen, MBL, Mitsubishi Tanabe, Mochida, Nippon Shinyaku, Novartis, Pfizer, Ono, Reata, Takeda, Teijin, and UCB (less than $10,000 each) and research grants from those companies. No other disclosures relevant to this article were reported.

Address correspondence to Masataka Kuwana, MD, PhD, Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan. Email: kuwanam@nms.ac.jp.

Submitted for publication September 21, 2019; accepted in revised form October 22, 2020.

## INTRODUCTION

Polymyositis/dermatomyositis (PM/DM) is characterized by the inflammation of skeletal muscles and skin. Patients with PM/DM often develop extramuscular manifestations, such as arthritis, cardiomyopathy, and interstitial lung disease (ILD) (1). Of these, ILD is one of the leading causes of mortality (2). The clinical course, response to treatment, and prognosis of PM/DM-ILD are highly variable among patients. For example, rapidly progressive ILD can occur over the course of days or weeks and is often refractory to immunosuppressive treatment, leading to death early in the disease course, while subacute ILD progresses over the course of weeks or months and often responds favorably to immunosuppressive treatment (3,4). Therefore, in the clinical setting, it is critical to predict the ILD course to pursue proper management.

A number of potential risk factors associated with poor ILD outcomes have been reported in PM/DM patients, and include demographic characteristics, physical findings, imaging features, and biomarkers (5–15). Of these, measurement of circulating biomarkers has the advantages of convenience and minimal invasiveness. Furthermore, biomarkers are not only correlated with clinical features, such as disease activity and severity, but are also closely involved in the pathophysiology of the disease (16).

In PM/DM patients, myositis-specific autoantibodies are the most reliable biomarker, i.e., patients with anti–melanoma differentiation–associated gene 5 (anti–MDA-5) antibody are more likely to develop rapidly progressive ILD with high mortality (4,6,8,13,17–19), while anti–aminoacyl transfer RNA synthetase (anti-ARS) antibodies are associated with subacute ILD, which frequently recurs after a reduction in treatment intensity (4). However, more than half of anti–MDA-5–positive patients with ILD survive (20,21), and rapidly progressive ILD can occur in patients with anti-ARS antibody (22). These findings clearly indicate that the presence or absence of myositis-specific autoantibodies alone is not sufficient to predict treatment response and mortality accurately. Nevertheless, higher anti–MDA-5 antibody levels measured by enzyme-linked immunosorbent assay (ELISA) were shown to correlate with poor outcomes (23).

Other circulating biomarkers reported to be associated with poor survival include C-reactive protein (CRP), ferritin, Krebs von den Lungen 6 (KL-6), surfactant protein D (SP-D), interferon-α (IFNα), tumor necrosis factor, interleukin-6 (IL-6), IL-8, IL-18, CXCL9, and CXCL10 levels (5,7,9–11,14,15,24–28). In this study, we aimed to establish a convenient risk stratification model based on a combination of initial serum biomarker levels using the large-scale Multicenter Retrospective Cohort of Japanese Patients with Myositis-Associated ILD (JAMI) (21).

## PATIENTS AND METHODS

**JAMI database.** This study used clinical information on 497 adult patients with PM, classic DM, or clinically amyopathic DM (CADM) who were enrolled in the JAMI database as a derivation cohort. Patients with ILD alone without any muscle involvement or hallmark cutaneous manifestation of DM were not included. JAMI is a multicenter, retrospective cohort of incident cases with PM/DM-ILD who visited participating centers between October 2011 and October 2015 (21). See Appendix A for a list of the JAMI investigators. The study protocol has been described in detail elsewhere (21). Briefly, all patients fulfilled the Bohan and Peter criteria for definite or probable PM/DM (29) or the Sontheimer criteria for CADM (30), except that patients were not required to meet the condition of no clinical evidence of myositis for at least 6 months. Demographic characteristics and clinical, laboratory, and imaging data at diagnosis prior to the initiation of immunosuppressive treatment as well as information on initial treatment regimens were collected anonymously in a dedicated electronic database. Information on survival and causes of death, if death occurred, was collected retrospectively and prospectively.

As a validation cohort, we additionally collected 111 adult incident cases with PM/DM-ILD who visited JAMI participating centers after enrollment into the original JAMI cohort had closed, using the same Bohan and Peter criteria (29) or Sontheimer criteria (30) for enrollment. The study protocol was approved by the Ethics Committee of the coordinating center (Nippon Medical School; 26-03-434) and by individual participating centers. The JAMI cohort was registered in the University Hospitals Medical Information Network Clinical Trial Registry (UMIN000018663).

**Serum biomarkers.** Anti–MDA-5 antibody, anti-ARS antibody, and CRP, ferritin, KL-6, and SP-D levels were chosen as candidate serum biomarkers for the prediction model for mortality, for the following reasons: 1) utility in predicting outcomes in PM/DM-ILD has been reported in the literature (9–12,15,20), and 2) assay systems have been established and validated for clinical use. Anti–MDA-5 antibody was measured using an in-house ELISA (17). Results are shown in units, and a cutoff level for positivity was set at 8 units. Anti-ARS antibody was identified using RNA immunoprecipitation assay (31). CRP, ferritin, KL-6, and SP-D levels were measured in the clinical laboratories of individual participating centers at the time of diagnosis.

**Statistical analysis.** All statistical analyses were performed by an independent medical statistician (KM) using SPSS Statistics version 23 (IBM), Prism 8.4.2 (GraphPad Software), JMP Pro 14.0.0 (SAS Institute), and R 3.4.3 (The R Foundation for Statistical Computing). Continuous values are shown as the median (2.5–97.5 percentile). Two patients who had both anti–MDA-5 and anti-ARS antibodies were included in both the

**Table 1.** Baseline characteristics and initial treatment of patients with PM/DM-ILD in the derivation and validation cohorts*

| | Derivation cohort (n = 497) | Validation cohort (n = 111) | *P* |
|---|---|---|---|
| Demographic characteristics | | | |
| Age at onset, years | 57 (29–80) | 55 (25–85) | 0.86 |
| Male sex, no. (%) | 167 (34) | 31 (28) | 0.25 |
| Disease duration at diagnosis, months | 3 (1–62)† | 3 (1–51) | 0.006 |
| Diagnosis, no. (%) | | | 0.04 |
| PM | 76 (15) | 10 (9) | |
| Classic DM | 158 (32) | 48 (43) | |
| CADM | 263 (53) | 53 (48) | |
| Laboratory parameters | | | |
| CK, IU/liter | 202 (32–4,267)‡ | 191 (26–8,212) | 0.96 |
| CRP, mg/dl | 0.7 (0.02–13.4)‡ | 0.81 (0.03–16.3) | 0.26 |
| Ferritin, ng/ml | 357 (22–3,846)§ | 386 (12–2,011) | 0.84 |
| KL-6, units/ml | 801 (208–4,431)¶ | 609 (183–2,828) | 0.0003 |
| SP-D, ng/ml | 91 (16–615)# | NA | – |
| Myositis-specific autoantibodies | | | |
| Anti–MDA-5 antibody, no. (%) | 209 (42)** | 60 (54) | 0.03 |
| Anti–MDA-5 antibody level, units | 106 (11–1,075) | NA | – |
| Anti-ARS antibody, no. (%) | 165 (33)†† | 46 (41) | 0.08 |
| Drugs used for initial treatment, no. (%) | | | |
| High-dose glucocorticoids | 289 (58) | 85 (77) | 0.0003 |
| Calcineurin inhibitors | 238 (48) | 98 (89) | <0.0001 |
| Cyclophosphamide | 223 (45) | 51 (46) | 0.84 |
| IVIG | 86 (17) | 19 (17) | 0.96 |

* Except where indicated otherwise, values are the median (2.5–97.5 percentile). PM/DM-ILD = polymyositis/dermatomyositis–associated interstitial lung disease; CADM = clinically amyopathic dermatomyositis; CK = creatine kinase; CRP = C-reactive protein; KL-6 = Krebs von den Lungen 6; SP-D = surfactant protein D; NA = not available; anti–MDA-5 = anti–melanoma differentiation–associated gene 5; anti-ARS = anti–aminoacyl transfer RNA synthetase; IVIG = intravenous immunoglobulin.
† Data were available for 495 patients (99.6%).
‡ Data were available for 486 patients (98%).
§ Data were available for 361 patients (73%).
¶ Data were available for 476 patients (96%).
# Data were available for 380 patients (76%).
** Data were available for 493 patients (99%).
†† Data were available for 489 patients (98%).

anti–MDA-5–positive and anti-ARS–positive groups. Multivariable analysis was conducted separately for the anti–MDA-5–positive and anti–MDA-5–negative groups. The cutoff values for the candidate biomarkers for all-cause mortality were determined using receiver operating characteristic (ROC) analysis with multivariable analysis. After assessing multicollinearity, dichotomous variables of biomarkers were applied to the Cox proportional hazards model to identify optimal models for predicting all-cause mortality. No continuous variable was applied to the multivariate analyses. The biomarkers selected by the Breslow test were used to determine the final Cox proportional hazards model. Stepwise backward deletion ($P \geq 0.10$) was performed using the Wald test to select the predictor variables in the model. To examine the impact of treatment on the prediction model, initial treatment agents, including high-dose glucocorticoids (prednisolone equivalent ≥50 mg daily), calcineurin inhibitors (cyclosporine or tacrolimus), cyclophosphamide, and intravenous immunoglobulin, were forcibly included in the final multivariable model as potential confounders.

To verify the original Cox proportional hazards models, a multiple imputation method was applied using 1,000 imputed data sets for all of the missing values of dichotomous variables. For multiple imputation, we used all dichotomous or categorical variables that were significant in a previous study (21). The results are presented as the hazard ratio (HR) and 95% confidence interval (95% CI). We then developed a prediction model for mortality using significant variables derived from the Cox proportional hazards model. Additionally, mortality rates were determined for each score from the original data set, and 95% CIs were calculated using bootstrap analysis with 1,000 resampling data sets. *P* values for multiple comparisons were adjusted using the Benjamini-Hochberg method. Cumulative survival rates were assessed using Kaplan-Meier analysis and were compared between subgroups by the Breslow test. *P* values less than 0.05 were considered significant.

## RESULTS

**Baseline patient characteristics and outcomes.** Selected baseline characteristics and initial treatment of patients in the derivation and validation cohorts are shown in Table 1. The median disease duration at diagnosis was 3 months in

**Table 2.** Cutoff values for initial serum biomarkers for predicting all-cause mortality in patients with PM/DM-ILD, stratified by the presence or absence of anti–MDA-5 antibody*

| Biomarker | Cutoff value† | Sensitivity/specificity,% | AUC | *P*‡ | No. of patients with data available |
|---|---|---|---|---|---|
| Anti–MDA-5–positive patients | | | | | |
| CRP, mg/dl | 0.8 | 75/59 | 0.734 | <0.001 | 206 |
| Ferritin, ng/ml | 1,000 | 43/79 | 0.681 | 0.001 | 168 |
| KL-6, units/ml | 1,000 | 78/44 | 0.717 | 0.009 | 204 |
| SP-D, ng/ml | 40 | 68/42 | 0.544 | 0.306 | 167 |
| Anti–MDA-5 antibody level, units | 180 | 45/70 | 0.624 | 0.027 | 209 |
| Anti–MDA-5–negative patients | | | | | |
| CRP, mg/dl | 1.1 | 68/65 | 0.682 | 0.002 | 276 |
| Ferritin, ng/ml | 300 | 44/67 | 0.694 | 0.274 | 191 |
| KL-6, units/ml | 1,000 | 79/62 | 0.689 | 0.003 | 268 |
| SP-D, ng/ml | 130 | 81/44 | 0.696 | 0.060 | 209 |

* AUC = area under the curve (see Table 1 for other definitions).
† Cutoff values were determined by the multivariable receiver operating characteristic curve.
‡ By Kaplan-Meier analysis with the Breslow test (for details, see Supplementary Figure 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41566/abstract).

both cohorts, indicating that most patients were diagnosed and treated at an early stage. Our cohort consisted mainly of patients with classic DM or CADM. In the derivation cohort, 91% of the patients fulfilled the 2017 European League against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies (32). Anti–MDA-5 and anti-ARS antibodies were detected in 42% and 33%, respectively, of the patients in the derivation cohort.

Ninety-three patients (19%) died during a median observation period of 20 months (range 1–50 months). The causes of death included respiratory insufficiency directly related to ILD in 76 patients (82%), infection in 5 patients (5%), malignancy in 5 patients (5%), and other causes, such as renal insufficiency, cardiomyopathy, and suicide, in 7 patients (8%), indicating that most of the patients in the JAMI cohort died directly of ILD. Of the 93 patients who died, 73 (78%) were positive for anti–MDA-5 antibody, clearly indicating that anti–MDA-5 antibody was the strongest predictor of mortality in the JAMI cohort. The major cause of mortality in anti–MDA-5–positive patients was respiratory insufficiency directly related to ILD (92%; n = 67).

**Identification of initial serum biomarkers useful for predicting mortality.** In the JAMI cohort, most of the patients who died were anti–MDA-5–positive (21). In fact, patients with anti–MDA-5 antibody had worse survival rates, and those with anti-ARS antibody had better survival rates, than patients without the antibodies ($P < 0.001$ for both comparisons) (Supplementary Figure 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41566/abstract). In particular, the survival rate decreased dramatically to 70% within 3 months after diagnosis for patients with anti–MDA-5 antibody. Therefore, we decided to develop prediction models for all-cause mortality in anti–MDA-5–positive and anti–MDA-5–negative patients independently.

As candidate serum biomarkers for predictors, CRP, ferritin, KL-6, SP-D, and anti–MDA-5 antibody levels were chosen for anti–MDA-5–positive patients, while CRP, ferritin, KL-6, SP-D levels, and anti-ARS antibody were chosen for anti–MDA-5–negative patients. The maximum variance inflation factors for serum biomarkers were 1.20 and 1.39 in anti–MDA-5–positive patients and anti–MDA-5–negative patients, respectively, indicating a lack of multicollinearity. We then conducted multivariable ROC analysis to determine optimal cutoff values for continuous variables, such as CRP, ferritin, KL-6, SP-D, and anti–MDA-5 antibody levels, for predicting all-cause mortality. The individual cutoff values were selected based on the highest area under the curve (AUC) and were rounded off (Table 2). Interestingly, optimal cutoff levels for serum biomarkers, except KL-6, differed between anti–MDA-5–positive and anti–MDA-5–negative patients, justifying the development of independent prediction models in patient subgroups stratified by the presence or absence of anti–MDA-5 antibody.

Kaplan-Meier curves were determined for patients with PM/DM-ILD stratified by the cutoff values for CRP, ferritin, KL-6, SP-D, and anti–MDA-5 antibody level (for anti–MDA-5–positive patients only), or the presence or absence of anti-ARS antibody (for anti–MDA-5–negative patients only) (Supplementary Figure 2, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41566/abstract). The cumulative survival rates were significantly different between the groups divided according to cutoff levels for CRP and KL-6 for both the anti–MDA-5–positive and anti–MDA-5–negative groups, while ferritin and anti–MDA-5 antibody levels were useful for the prediction of survival only in patients with anti–MDA-5 antibody.

To select serum biomarkers for the prediction models, all candidate biomarkers, i.e., CRP, ferritin, KL-6, and anti–MDA-5

**Table 3.** Initial serum biomarkers for predicting all-cause mortality in patients with PM/DM-ILD, stratified by the presence or absence of anti–MDA-5 antibody*

| | Crude | | Adjusted for treatment | | Multiple imputation | | Multiple imputation and adjusted for treatment | |
|---|---|---|---|---|---|---|---|---|
| Serum biomarker | HR (95% CI) | *P* | HR (95% CI) | *P* | HR (95% CI) | *P* | HR (95% CI) | *P* |
| Anti–MDA-5–positive patients† | | | | | | | | |
| CRP ≥0.8 mg/dl | 3.1 (1.8–5.3) | <0.001 | 2.5 (1.4–4.3) | 0.001 | 3.2 (1.9–5.5) | <0.001 | 2.6 (1.5–4.6) | 0.001 |
| KL-6 ≥1,000 units/ml | 1.7 (1.0–2.7) | 0.033 | 1.8 (1.1–2.9) | 0.012 | 1.7 (1.0–2.7) | 0.031 | 1.8 (1.1–2.9) | 0.011 |
| Anti–MDA-5–negative patients‡ | | | | | | | | |
| CRP ≥1.1 mg/dl | 3.7 (1.3–10.1) | 0.011 | 4.9 (1.8–13.5) | 0.002 | 3.8 (1.4–10.0) | 0.007 | 4.9 (1.8–13.5) | 0.002 |
| KL-6 ≥1,000 units/ml | 3.6 (1.2–11.3) | 0.017 | 6.1 (1.9–19.8) | 0.003 | 5.7 (1.9–17.2) | 0.002 | 6.0 (1.8–19.8) | 0.003 |

* Hazard ratios (HRs), 95% confidence intervals (95% CIs), and *P* values were obtained by Cox proportional hazards model using CRP level and KL-6 as explanatory variables. See Table 1 for other definitions.
† n = 203; n = 209 for multiple imputation.
‡ n = 267; n = 284 for multiple imputation.

antibody levels for anti–MDA-5–positive patients, and CRP and KL-6 levels for anti–MDA-5–negative patients, were subjected to Cox regression analysis as potential explanatory variables. Through stepwise backward deletion, we finally selected CRP and KL-6 levels as significant independent risk factors for all-cause mortality in both anti–MDA-5–positive and anti–MDA-5–negative patients. Sensitivity analysis showed that statistical significance was consistent among different models adjusted for initial treatment regimens and/or complementation of the missing data by multiple imputation (Table 3).

**Predictive modeling for mortality based on a combination of serum biomarkers.** We then generated a predictive model for all-cause mortality based on the levels at diagnosis of a combination of independent serum biomarkers, in anti–MDA-5–positive and anti–MDA-5–negative patients separately (CRP ≥0.8 mg/dl and KL-6 ≥1,000 units/ml for anti–MDA-5–positive patients, and CRP ≥1.1 mg/dl and KL-6 ≥1,000 units/ml for anti–MDA-5–negative patients) (Table 4). When the risk score was defined as the number of risk factors, the mortality rates for patients with risk scores of 0, 1, and 2 were 13.6%, 39.2%, and 57.5%, respectively, in anti–MDA-5–positive patients. In this 3-group model, the 95% CIs of the mortality rates estimated by the bootstrap method were separated with minimum overlap among the subgroups. However, in anti–MDA-5–negative patients, observed mortality rates for patients with risk scores of 0, 1, and 2 were 2.0%, 4.7%, and 27.5%, respectively. The 95% CIs of the mortality rates estimated by the bootstrap method had an apparent overlap between patients with a score of 0 and those with a score of 1. Therefore, we combined the patients with a risk score of 0 and those with a risk score of 1 to create a 2-group model, resulting in good separation of the 95% CIs between the 2 groups. Given these results, we built a prognostic matrix model, based

**Table 4.** All-cause mortality rates by the risk score observed in the cohort and estimated by the bootstrap method, stratified by the presence or absence of anti–MDA-5 antibody*

| Risk score† | Observed mortality rate, % | Mortality rate estimated by the bootstrap method, median % (95% CI) |
|---|---|---|
| Anti–MDA-5–positive patients (3-group model) | | |
| 0 (n = 66) | 13.6 | 13.4 (6.0–22.2) |
| 1 (n = 97) | 39.2 | 39.9 (30.0–50.0) |
| 2 (n = 40) | 57.5 | 57.5 (43.1–73.0) |
| Anti–MDA-5–negative patients (3-group model) | | |
| 0 (n = 100) | 2.0 | 1.9 (0.0–5.3) |
| 1 (n = 127) | 4.7 | 4.5 (1.5–8.5) |
| 2 (n = 40) | 27.5 | 27.1 (13.9–41.7) |
| Anti–MDA-5–negative patients (2-group model) | | |
| 0 or 1 (n = 227) | 3.5 | 3.1 (0.0–7.8) |
| 2 (n = 40) | 27.5 | 27.1 (13.9–41.7) |

* 95% CI = 95% confidence interval (see Table 1 for other definitions).
† Number of individual risk factors (CRP level ≥0.8 mg/dl and KL-6 ≥1,000 units/ml for anti–MDA-5–positive patients, and CRP level ≥1.1 mg/dl and KL-6 ≥1,000 units/ml for anti–MDA-5–negative patients).

on anti–MDA-5 antibody, CRP level, and KL-6 level, termed "MCK model," identifying patients with PM/DM-ILD at low (<15%), moderate (15–50%), or high (≥50%) risk of mortality during the follow-up period (Figure 1A).

Kaplan-Meier analysis with the Breslow test revealed that the survival curves were significantly differentiated between anti–MDA-5–positive patients stratified by risk score, confirming the validity of this 3-group model (Figure 1C). In anti–MDA-5–negative patients, there was no difference in the cumulative survival rates between patients with a score of 0 and those with a score of 1 in the 3-group model, but differentiation of survival curves in the 2-group model was excellent (Figure 1E). When we divided anti–MDA-5–positive patients into 2 groups based on antibody level (≥180 units and <180 units), survival curves differed according to the MCK model score in both groups, but the MCK model performed better in patients with anti–MDA-5 antibody level <180 units (Supplementary Figure 3, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41566/abstract). Concordant results were obtained when these models were tested for mortality due to respiratory insufficiency directly related to ILD instead of all-cause mortality (Supplementary Figure 4, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41566/abstract).

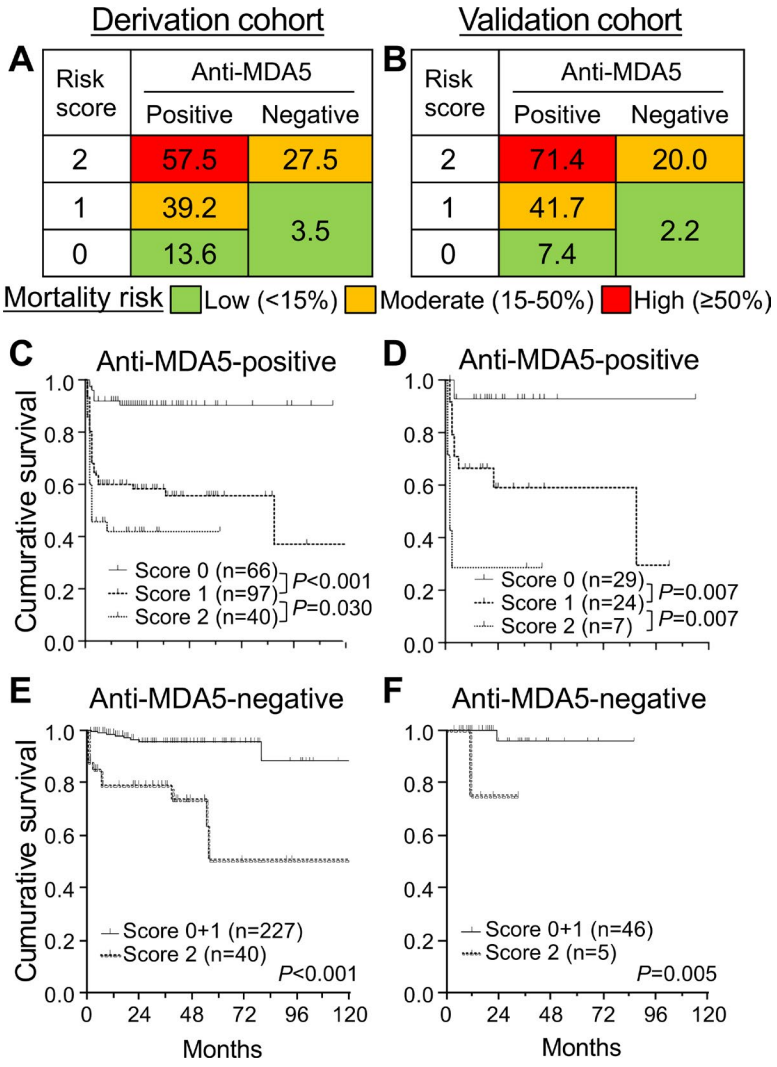


**Figure 1.** A model of mortality risk in patients with polymyositis/dermatomyositis–associated interstitial lung disease (PM/DM-ILD) based on anti–melanoma differentiation–associated gene 5 (anti–MDA-5) antibody status, C-reactive protein (CRP) level, and Krebs von den Lungen 6 (KL-6) (the MCK matrix model), and cumulative survival rates in patients with PM/DM-ILD classified by risk score. The risk score was defined as the number of risk factors (CRP ≥0.8 mg/dl and KL-6 ≥1,000 units/ml for anti–MDA-5–positive patients, and CRP ≥1.1 mg/dl and KL-6 ≥ 1,000 units/ml for anti–MDA-5–negative patients). **A** and **B**, The MCK matrix model of mortality risk (low, moderate, or high) based on the risk score and anti–MDA-5 antibody status in the derivation cohort (**A**) and validation cohort (**B**). Values in the matrices are the rates of all-cause mortality. **C** and **D**, Survival curves using the 3-group model for anti–MDA-5–positive patients in the derivation cohort (**C**) and validation cohort (**D**). **E** and **F**, Survival curves using the 2-group model for anti–MDA-5–negative patients in the derivation cohort (**E**) and validation cohort (**F**). Survival curves were determined by Kaplan-Meier analysis with the Breslow test.

**Table 5.** Performance of the MCK model compared with anti–MDA-5 antibody testing alone in predicting mortality in patients with PM/DM-ILD*

| | Sensitivity | Specificity | PPV | NPV | Accuracy |
|---|---|---|---|---|---|
| All-cause mortality (n = 470) | | | | | |
| Anti–MDA-5 antibody testing alone | 79 | 65 | 35 | 93 | 68 |
| MCK model | | | | | |
| Low risk | 81 | 73 | 41 | 94 | 74 |
| High risk | 26 | 96 | 58 | 84 | 82 |
| Mortality due to ILD (n = 470) | | | | | |
| Anti–MDA-5 antibody testing alone | 88 | 66 | 32 | 97 | 69 |
| MCK model | | | | | |
| Low risk | 87 | 72 | 37 | 97 | 74 |
| High risk | 29 | 95 | 55 | 88 | 85 |

* Risk stratification in the MDA-5, CRP, and KL-6 (MCK) model was determined based on the prognostic matrix model shown in Figure 1. Values are the percent. PPV = positive predictive value; NPV = negative predictive value (see Table 1 for other definitions).

The performance of the MCK model for predicting mortality in patients with PM/DM-ILD was compared with anti–MDA-5 antibody testing alone (Table 5). Anti–MDA-5 antibody testing was a binary variable and had a sensitivity of 79%, specificity of 65%, positive predictive value (PPV) of 35%, negative predictive value of 93%, and accuracy of 68% for all-cause mortality. In contrast, the MCK model enabled us to divide the patients into 3 risk groups: high risk, moderate risk, and low risk. Identification of patients with low risk resulted in increased sensitivity and specificity (81% and 73%, respectively) without decreases in other indices. When patients with high risk were selected, specificity was increased to 96% with a PPV of 58% and accuracy of 82%. Almost concordant findings were observed when we evaluated the risk of mortality due to ILD. These findings suggest improvement of risk stratification in patients with PM/DM-ILD using the MCK model.

**Validation of the MCK model in a validation cohort.** An independent validation cohort consisting of 111 adult incident cases of PM/DM-ILD was used to assess the reproducibility of the MCK model for the prediction of mortality risk. In the validation cohort, 19 patients (17%) died during a median of 21 months. The baseline characteristics were similar between the cohorts, while anti–MDA-5 antibody was more prevalent and the patients were treated more intensively in the validation cohort than in the derivation cohort (Table 1). The prognostic MCK matrix model developed in the derivation cohort was principally replicated in the validation cohort (Figure 1B). In addition, cumulative survival rates stratified by the MCK model were principally similar to those in the derivation cohort (Figures 1D and F).

**Simplified MCK model.** In the MCK model, different cutoff levels for CRP were applied for anti–MDA-5–positive and anti–MDA-5–negative patients (0.8 and 1.1 mg/dl, respectively). To make the modeling more convenient, the optimal cutoff level for CRP for the entire cohort was investigated using ROC analysis, and found to be 1.0 mg/dl (AUC 0.704). The simplified MCK model using CRP ≥1.0 mg/dl and KL-6 ≥1,000 units/ml for all patients with PM/DM-ILD showed acceptable performance in terms of discrimination of cumulative survival rates in both anti–MDA-5–positive and anti–MDA-5–negative patients (Supplementary Figure 5, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41566/abstract).

## DISCUSSION

We successfully developed an evidence-based MCK risk stratification model for mortality in patients with PM/DM-ILD, based on a combination of serum biomarkers measured at diagnosis. Anti–MDA-5 antibody was the strongest predictor of poor survival in patients with PM/DM-ILD in the JAMI cohort (21), but we showed that the additional measurement of CRP and KL-6 levels enhanced the accuracy for predicting outcomes. Interestingly, the same predictors, CRP and KL-6 levels, were identified in both anti–MDA-5–positive and anti–MDA-5–negative patients, resulting in the development of the simplified, convenient modeling. The MCK model has several advantages over anti–MDA-5 antibody testing alone: it provides more detailed risk stratification by dividing patients into 3 risk groups, and it enables us to subdivide mortality risk by anti–MDA-5 antibody status. A strength of our study is the consistency of the utility of the MCK model across independent derivation and validation cohorts, which were selected in different treatment eras. However, the MCK model still needs to be validated in prospective studies involving various patient populations.

The MCK model is potentially useful in clinical practice for predicting prognosis and deciding on treatment regimens for patients newly diagnosed as having PM/DM-ILD. Since the predictors used for the MCK model remained significant even after adjustment for treatment, therapeutic regimens had little impact on the prediction of mortality risk. Up-front aggressive immunosuppression consisting of high-dose glucocorticoids and a combination of immunosuppressants was used for the treatment of DM-ILD based solely

on anti–MDA-5 antibody positivity (33), but severe infection while receiving excessive immunosuppression is reported to be a critical prognostic factor in this patient population (34). Since the MCK model was able to identify patients with a low risk of mortality, it might provide information useful to avoid unnecessary excessive immunosuppression in such patients. The MCK model identified patients with a high mortality risk with a specificity of 96%. These patients should be treated with aggressive immunosuppression, and might be eligible for clinical trials of potential novel treatments, such as tofacitinib (35) and plasma exchange (36). Taken together, these findings indicate that the MCK model could contribute to personalized medicine in patients with PM/DM-ILD (37).

Our prediction model was able to identify patients with moderate mortality risk in the anti–MDA-5–negative patient subset, although its proportion was relatively small (15% and 10% in the derivation and validation cohorts, respectively). In the JAMI cohort, anti-ARS antibody had less prognostic value in anti–MDA-5–negative patients. Rapidly progressive ILD can occur in patients with antisynthetase syndrome, but there is no reliable predictor of poor prognosis (22,38), indicating the value of the MCK model in anti–MDA-5–negative patients with PM/DM-ILD.

The independent risk factors for mortality identified in this study are not only biomarkers, but also may reflect the ongoing pathogenic process of PM/DM-ILD. MDA-5 is a sensor for double-stranded RNA viruses such as picornavirus, and is involved in the synthesis of type I IFN and the activation of NF-κB (39). The pathogenic contribution of the anti–MDA-5 antibody itself is not well documented, but a recent study suggested that anti–MDA-5 antibodies induce epithelial cell injury and a resultant release of inflammatory cytokines by promoting the formation of neutrophil extracellular traps (40). A high titer of anti–MDA-5 antibody was shown to correlate with poor treatment outcomes in patients with PM/DM-ILD (22,41,42), but our study failed to show that anti–MDA-5 antibody level was an independent predictor of mortality.

The level of CRP produced, which is under the control of IL-6 signaling (43), has been shown to be associated with disease activity and poor prognosis in patients with PM/DM-ILD (44–46). KL-6 is a mucin-like, high molecular weight glycoprotein expressed mainly on the surface membrane of type 2 alveolar pneumocytes, and an elevated level of circulating KL-6 is thought to result from the injury of alveolar cells and the destruction of vasculature in the lungs (47,48). Interestingly, CRP and KL-6 were identified as risk factors for mortality independent of anti–MDA-5 antibody status. Therefore, the biomarkers identified may reflect ongoing pathogenic processes of PM/DM-ILD, including injury of alveolar epithelium and vasculature, and the activation of inflammatory cytokine pathways.

There were several limitations to this study. First, the participating centers of the JAMI cohort consist mainly of tertiary referral hospitals, which were likely to enroll patients with more severe disease. In fact, patients with anti–MDA-5 antibodies dominated the JAMI cohort, but a series of analyses indicated that CRP and KL-6 levels were predictors of mortality independent of anti–MDA-5 antibody positivity. Second, JAMI did not enroll patients with anti-ARS antibody without any muscle or skin symptoms. This is simply because JAMI protocol was established in 2011 when measurement of anti-ARS and anti–MDA-5 antibodies was not routinely feasible in clinical practice and thus was not part of the inclusion criteria. Expansion of the disease spectrum of PM/DM-ILD and inclusion of antisynthetase syndrome should be an interesting future research agenda. Third, candidate serum biomarkers were selected based on availability in the JAMI database, and were not chosen from a large panel of potential biomarkers. Finally, measurement of KL-6 level is currently available in clinical practice only in some countries. Nevertheless, there is accumulating evidence showing the utility of KL-6 as a biomarker for diagnosis, and for the prediction of disease progression, prognosis, and treatment response in patients with various types of ILD, especially those with a progressive phenotype and poor outcomes, such as idiopathic pulmonary fibrosis and ILD associated with systemic sclerosis, rheumatoid arthritis, and PM/DM (49,50), supporting widespread use of KL-6 measurement in routine clinical practice.

In conclusion, we successfully established the MCK risk stratification model using serum biomarkers in patients with PM/DM-ILD using data from a large cohort. The MCK model might help physicians decide how to manage patients with newly diagnosed PM/DM-ILD, and could be also useful for cohort enrichment in future clinical trials.

## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Kuwana had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Gono, Masui, Nishina, Sato, Kuwana.
**Acquisition of data.** Gono, Masui, Nishina, Kawaguchi, Kawakami, Ikeda, Kirino, Sugiyama, Tanino, Nunokawa, Kaneko, Sato, Asakawa, Ukichi, Kaieda, Naniwa, Okano, Kuwana.
**Analysis and interpretation of data.** Masui.

## REFERENCES

1. Lundberg IE, de Visser M, Werth VP. Classification of myositis [review]. Nat Rev Rheumatol 2018;14:269–78.
2. Marie I. Morbidity and mortality in adult polymyositis and dermatomyositis. Curr Rheumatol Rep 2012;14:275–85.
3. Kawasumi H, Gono T, Kawaguchi Y, Yamanaka H. Recent treatment of interstitial lung disease with idiopathic inflammatory myopathies. Clin Med Insights Circ Respir Pulm Med 2015;9 Suppl:9–17.
4. Gono T, Kuwana M. Inflammatory myopathies: choosing the right biomarkers to predict ILD in myositis [review]. Nat Rev Rheumatol 2016;12:504–6.
5. Takada T, Suzuki E, Nakano M, Kagamu H, Tsukada H, Hasegawa T, et al. Clinical features of polymyositis/dermatomyositis with steroid-resistant interstitial lung disease. Intern Med 1998;37:669–73.
6. Selva-O'Callaghan A, Labrador-Horrillo M, Muñoz-Gall X, Martínez-Gomez X, Majó-Masferrer J, Solans-Laque R, et al. Polymyositis/

dermatomyositis-associated lung disease: analysis of a series of 81 patients. Lupus 2005;14:534–42.
7. Cao H, Xia Q, Pan M, Zhao X, Li X, Shi R, et al. Gottron papules and Gottron sign with ulceration: a distinctive cutaneous feature in a subset of patients with classic dermatomyositis and clinically amyopathic dermatomyositis. J Rheumatol 2016;43:1735–42.
8. Sato S, Hirakata M, Kuwana M, Suwa A, Inada S, Mimori T, et al. Autoantibodies to a 140-kd polypeptide, CADM-140, in Japanese patients with clinically amyopathic dermatomyositis. Arthritis Rheum 2005;52:1571–6.
9. Gono T, Kawaguchi Y, Satoh T, Kuwana M, Katsumata Y, Takagi K, et al. Clinical manifestation and prognostic factor in anti-melanoma differentiation-associated gene 5 antibody-associated interstitial lung disease as a complication of dermatomyositis. Rheumatology (Oxford) 2010;49:1713–9.
10. Xu Y, Yang CS, Li YJ, Liu XD, Wang JN, Zhao Q, et al. Predictive factors of rapidly progressive-interstitial lung disease in patients with clinically amyopathic dermatomyositis. Clin Rheumatol 2016; 35:113–6.
11. Arai S, Kurasawa K, Maezawa R, Owada T, Okada H, Fukuda T. Marked increase in serum KL-6 and surfactant protein D levels during the first 4 weeks after treatment predicts poor prognosis in patients with active interstitial pneumonia associated with polymyositis/dermatomyositis. Mod Rheumatol 2013;23:872–83.
12. Hozumi H, Fujisawa T, Nakashima R, Johkoh T, Sumikawa H, Murakami A, et al. Comprehensive assessment of myositis-specific autoantibodies in polymyositis/dermatomyositis-associated interstitial lung disease. Respir Med 2016;121:91–9.
13. Koga T, Fujikawa K, Horai Y, Okada A, Kawashiri SY, Iwamoto N, et al. The diagnostic utility of anti-melanoma differentiation-associated gene 5 antibody testing for predicting the prognosis of Japanese patients with DM. Rheumatology (Oxford) 2012;51:1278–84.
14. Tanizawa K, Handa T, Nakashima R, Kubo T, Hosono Y, Aihara K, et al. The prognostic value of HRCT in myositis-associated interstitial lung disease. Respir Med 2013;107:745–52.
15. Fujiki Y, Kotani T, Isoda K, Ishida T, Shoda T, Yoshida S, et al. Evaluation of clinical prognostic factors for interstitial pneumonia in anti-MDA5 antibody-positive dermatomyositis patients. Mod Rheumatol 2018;28:133–40.
16. Jog NR, James JA. Biomarkers in connective tissue diseases. J Allergy Clin Immunol 2017;140:1473–83.
17. Sato S, Hoshino K, Satoh T, Fujita T, Kawakami Y, Kuwana M. RNA helicase encoded by melanoma differentiation–associated gene 5 is a major autoantigen in patients with clinically amyopathic dermatomyositis: association with rapidly progressive interstitial lung disease. Arthritis Rheum 2009;60:2193–200.
18. Moghadam-Kia S, Oddis CV, Sato S, Kuwana M, Aggarwal R. Anti–melanoma differentiation–associated gene 5 is associated with rapidly progressive lung disease and poor survival in US patients with amyopathic and myopathic dermatomyositis. Arthritis Care Res (Hoboken) 2016;68:689–94.
19. Moghadam-Kia S, Oddis CV, Sato S, Kuwana M, Aggarwal R. Antimelanoma differentiation-associated gene 5 antibody: expanding the clinical spectrum in North American patients with dermatomyositis. J Rheumatol 2017;44:319–25.
20. Gono T, Sato S, Kawaguchi Y, Kuwana M, Hanaoka M, Katsumata Y, et al. Anti-MDA5 antibody, ferritin and IL-18 are useful for the evaluation of response to treatment in interstitial lung disease with anti-MDA5 antibody-positive dermatomyositis. Rheumatology (Oxford) 2012;51:1563–70.
21. Sato S, Masui K, Nishina N, Kawaguchi Y, Kawakami A, Tamura M, et al. Initial predictors of poor survival in myositis-associated interstitial lung disease: a multicentre cohort of 497 patients. Rheumatology (Oxford) 2018;57:1212–21.
22. Huang K, Aggarwal R. Antisynthetase syndrome: a distinct disease spectrum. J Scleroderma Relet Disord 2020;5:178–91.
23. Sato S, Kuwana M, Fujita T, Suzuki Y. Anti-CADM-140/MDA5 autoantibody titer correlates with disease activity and predicts disease outcome in patients with dermatomyositis and rapidly progressive interstitial lung disease. Mod Rheumatol 2013;23: 496–502.
24. Zhang L, Wu G, Gao D, Liu G, Pan L, Ni L, et al. Factors associated with interstitial lung disease in patients with polymyositis and dermatomyositis: a systematic review and meta-analysis. PLoS One 2016;11:e0155381.
25. Horai Y, Koga T, Fujikawa K, Takatani A, Nishino A, Nakashima Y, et al. Serum interferon-α is a useful biomarker in patients with anti-melanoma differentiation-associated gene 5 (MDA5) antibody-positive dermatomyositis. Mod Rheumatol 2015;25:85–9.
26. Kawasumi H, Gono T, Kawaguchi Y, Kaneko H, Katsumata Y, Hanaoka M, et al. IL-6, IL-8, and IL-10 are associated with hyperferritinemia in rapidly progressive interstitial lung disease with polymyositis/dermatomyositis. Biomed Res Int 2014;2014:815245.
27. Richards TJ, Eggebeen A, Gibson K, Yousem S, Fuhrman C, Gochuico BR, et al. Characterization and peripheral blood biomarker assessment of anti–Jo-1 antibody–positive interstitial lung disease. Arthritis Rheum 2009;60:2183–92.
28. Zou J, Chen J, Yan Q, Guo Q, Bao C. Serum IL8 and mRNA level of CD11b in circulating neutrophils are increased in clinically amyopathic dermatomyositis with active interstitial lung disease. Clin Rheumatol 2016;35:117–25.
29. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med 1975;292:344–7.
30. Sontheimer RD. Would a new name hasten the acceptance of amyopathic dermatomyositis (dermatomyositis siné myositis) as a distinctive subset within the idiopathic inflammatory dermatomyopathies spectrum of clinical illness? J Am Acad Dermatol 2002;46:626–36.
31. Forman MS, Nakamura M, Mimori T, Gelpi C, Hardin JA. Detection of antibodies to small nuclear ribonucleoproteins and small cytoplasmic ribonucleoproteins using unlabeled cell extracts. Arthritis Rheum 1985;28:1356–61.
32. Lundberg IE, Tjärnlund A, Bottai M, Werth VP, Pilkington C, de Visser M, et al. 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. Arthritis Rheumatol 2017;69:2271–82.
33. Tsuji H, Nakashima R, Hosono Y, Imura Y, Yagita M, Yoshifuji H, et al. Multicenter prospective study of the efficacy and safety of combined immunosuppressive therapy with high-dose glucocorticoid, tacrolimus, and cyclophosphamide in interstitial lung diseases accompanied by anti–melanoma differentiation–associated gene 5–positive dermatomyositis. Arthritis Rheumatol 2020;72:488–98.
34. Sugiyama Y, Yoshimi R, Tamura M, Takeno M, Kunishita Y, Kishimoto D, et al. The predictive prognostic factors for polymyositis/dermatomyositis-associated interstitial lung disease. Arthritis Res Ther 2018;20:7.
35. Chen Z, Wang X, Ye S. Tofacitinib in amyopathic dermatomyositis-associated interstitial lung disease. N Engl J Med 2019;381: 291–93.
36. Shirakashi M, Nakashima R, Tsuji H, Tanizawa K, Handa T, Hosono Y, et al. Efficacy of plasma exchange in anti-MDA5-positive dermatomyositis with interstitial lung disease under combined immunosuppressive treatment. Rheumatology (Oxford) 2020;59:3284–92.

37. Romero-Bueno F, del Campo PD, Trallero-Araguás E, Ruiz-Rodríguez JC, Castellvi I, Rodriguez-Nieto MJ, et al. Recommendations for the treatment of anti-melanoma differentiation-associated gene 5-positive dermatomyositis-associated rapidly progressive interstitial lung disease. Semin Arthritis Rheum 2020;50:776–90.
38. Vuillard C, de Chambrun MP, de Prost N, Guérin C, Schmidt M, Dargent A, et al. Clinical features and outcome of patients with acute respiratory failure revealing anti-synthetase or anti-MDA-5 dermato-pulmonary syndrome: a French multicenter retrospective study. Ann Intensive Care 2018;8:87.
39. Takeuchi O, Akira S. MDA5/RIG-I and virus recognition. Curr Opin Immunol 2008;20:17–22.
40. Peng Y, Zhang S, Zhao Y, Liu Y, Yan B. Neutrophil extracellular traps may contribute to interstitial lung disease associated with anti-MDA5 autoantibody positive dermatomyositis. Clin Rheumatol 2018;37:107–15.
41. Sato S, Kuwana M, Fujita T, Suzuki Y. Amyopathic dermatomyositis developing rapidly progressive interstitial lung disease with elevation of anti-CADM-140/MDA5 autoantibodies. Mod Rheumatol 2012;22:625–9.
42. Sato S, Murakami A, Kuwajima A, Takehara K, Mimori T, Kawakami A, et al. Clinical utility of an enzyme-linked immunosorbent assay for detecting anti-melanoma differentiation-associated gene 5 autoantibodies. PLoS One 2016;11:e0154285.
43. Deichmann M, Benner A, Waldmann V, Bock M, Jäckel A, Näher H. Interleukin-6 and its surrogate C-reactive protein are useful serum markers for monitoring metastasized malignant melanoma. J Exp Clin Cancer Res 2000;19:301–7.
44. Gono T, Kawaguchi Y, Hara M, Masuda I, Katsumata Y, Shinozaki M, et al. Increased ferritin predicts development and severity of acute interstitial lung disease as a complication of dermatomyositis. Rheumatology (Oxford) 2010;49:1354–60.
45. Gono T, Kawaguchi Y, Ozeki E, Ota Y, Satoh T, Kuwana M, et al. Serum ferritin correlates with activity of anti-MDA5 antibody-associated acute interstitial lung disease as a complication of dermatomyositis. Mod Rheumatol 2011;21:223–7.
46. Isoda K, Takeuchi T, Kotani T, Hata K, Shoda T, Ishida T, et al. Pretreatment ferritin level and alveolar-arterial oxygen gradient can predict mortality rate due to acute/subacute interstitial pneumonia in dermatomyositis treated by cyclosporine a/glucocorticosteroid combination therapy: a case control study. PLoS One 2014;9:e89610.
47. Kohno N, Kyoizumi S, Awaya Y, Fukuhara H, Yamakido M, Akiyama M. New serum indicator of interstitial pneumonitis activity. Sialylated carbohydrate antigen KL-6. Chest 1989;96:68–73.
48. Ishikawa N, Hattori N, Yokoyama A, Kohno N. Utility of KL-6/MUC1 in the clinical management of interstitial lung diseases. Respir Investig 2012;50:3–13.
49. Chiba H, Otsuka M, Takahashi H. Significance of molecular biomarkers in idiopathic pulmonary fibrosis: a mini review. Respir Investig 2018;56:384–91.
50. Inoue Y, Kaner RJ, Guiot J, Maher TM, Tomassetti S, Moiseev S, et al. Diagnostic and prognostic biomarkers for chronic fibrosing interstitial lung diseases with a progressive phenotype. Chest 2020;158:646–59.

## APPENDIX A: THE JAMI INVESTIGATORS

The JAMI Investigators are as follows: Yukie Yamaguchi (Yokohama City University Graduate School of Medicine), Yoshinori Taniguchi (Kochi Medical School, Kochi University), Jun Kikuchi (Saitama Medical Center, Saitama Medical University), Makoto Kubo (Yamaguchi University Graduate School of Medicine), Masaki Watanabe (Graduate School of Medical and Dental Sciences, Kagoshima University), Tatsuhiko Harada (Nagasaki University School of Medicine), Taisuke Kazuyori (The Jikei University School of Medicine Katsushika Medical Center), Hideto Kameda (Toho University Ohashi Medical Center), Makoto Kaburaki (Toho University School of Medicine), Yasuo Matsuzawa (Toho University Medical Center, Sakura Hospital), Shunji Yoshida (Fujita Health University School of Medicine), Yasuko Yoshioka (Juntendo University Urayasu Hospital), Takuya Hirai (Juntendo University Urayasu Hospital), Yoko Wada (Niigata University Graduate School of Medical and Dental Sciences), Koji Ishii (Faculty of Medicine, Oita University), Sakuhei Fujiwara (Faculty of Medicine, Oita University), Takeshi Saraya (Kyorin University), Kozo Morimoto (Fukujuji Hospital, Japan Anti-Tuberculosis Association), Tetsu Hara (Hiratsuka Kyosai Hospital), Hiroki Suzuki (Saiseikai Yamagata Saisei Hospital), Hideki Shibuya (Tokyo Teishin Hospital), Yoshinao Muro (Nagoya University Graduate School of Medicine), Ryoichi Aki (Kitasato University School of Medicine), Takuo Shibayama (National Hospital Organization Okayama Medical Center), Shiro Ohshima (National Hospital Organization Osaka Minami Medical Center), Yuko Yasuda (Saiseikai Kumamoto Hospital), Masaki Terada (Saiseikai Niigata Daini Hospital), and Yoshie Kawahara (Keiyu Hospital).